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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/726,258	11/29/2000	Vanessa Hsei	P1085R4-1AC1	4895

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EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/726,258	HSEI ET AL.	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,20,25,26,28,29 and 31-36* is/are pending in the application.

4a) Of the above claim(s) *20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,25,26,28,29 and 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 12/30/02 (Paper No. 12), is acknowledged.
Claims 2-19, 21-24, 27 and 30 have been cancelled.
Claim 36 has been added.
Claims 1, 20, 25 and 26 have been amended.
Claims 1, 20, 25-26, 28-29 and 31-36 are pending.

Claim 20 stands withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species.

Claims 1, 25-26, 28-29 and 31-36 *are under consideration in the instant application.*

2. This Office Action will be in response to applicant's arguments, filed 12/30/02 (Paper No. 12). The rejections of record can be found in the previous Office Action (Paper No. 10).

It is noted that New Grounds of Rejection are set forth herein.

3. Applicant's cancellation of claims 5, 8, 10-19, 21, 24 and 30 has obviated the previous objections and rejections with respect to these claims.

Drawings

4. Applicant's petition filed under 37 CFR 1.84(a)(2) has been granted permitting their use as acceptable drawings, see Paper No. 13 attached hereto.

IDS

5. Applicant's re-provision of the references cited on the IDS filed 11/29/00 (Paper No. 5), in parent application USSN 09/234,182 is gratefully acknowledged.

These references have now been considered as shown by initialing on the attached copy of form PTO-1449.

Specification

6. Applicant's correction of the ATCC address on page 188 at lines 3 and 14 is acknowledged. However, the ATCC address should also be corrected on page 240 in the paragraph beginning at line 21 (as amended on 12/30/02).

Applicant is reminded that the current address of the ATCC is:
American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.

Applicant is requested to review the specification to determine if the incorrect address occurs elsewhere.

Claim Rejections - 35 USC § 112 second paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 25-26, 28-29 and 31-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments, filed 12/30/02, have been fully considered but have not been found convincing.

Applicant argues that the term "consisting essentially of" is not indefinite when applied to a compound claim because in the instant case the conjugate is understood to necessarily include the Fab' and PEG components, but might additionally have modifications which do not materially affect the properties of the conjugate.

However, the instant claims appear to draw a distinction between "consisting essentially of" claim language and "comprising" claim language which renders the instant use of the "consisting essentially of" transitional phrase ambiguous and indefinite. The Examiner maintains that it is not clear what elements are encompassed that would not affect the basic characteristics of the recited compound.

It is suggested that Applicant amend the claims to simply recite "comprising".

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

35 USC § 112 first paragraph

9. Applicant's amendment has obviated the previous rejection of claims 1, 5, 8, 10-19, 21, 26 and 28-35 under 35 U.S.C. 112, first paragraph, by limiting the pending claims to an enabled embodiment.

Claim Rejections – 35 U.S.C. §§ 102 and 103

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1, 25-26, 28-29 and 31-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Gonzalez et a. (U.S. Patent No. 6,133,426, of record, see entire document).

Applicant argues that a Declarations under 37 CFR 1.132 by Leonard Presta and Steven Leong establishes that the cited patent is not "by another".

However, no Declarations under 37 CFR 1.132 were found attached to the instant Reply and no such Declarations are of record in the instant case.

In addition, it is not clear from Applicant's comments if the Declarations were intended to be provided with respect to U.S. Patent No. 6,133,426, U.S. Patent No. 6,025,158, or both.

In the absence of the referenced Declarations, Applicant's argument that "the cited patent" is not "by another" is not found convincing.

The rejection of record is reiterated below as now applied to the amended claims:

Gonzales et al. teach a conjugate comprising an antibody Fab' (Fab'-SH) covalently attached to a single PEG molecule, wherein the PEG has an average molecular weight of at least about 20kD (see especially example T at columns 121-123) Gonzales et al. also teach that the conjugate of an antibody Fab' fragment and a single PEG is a conjugate that has an apparent size of at least about 500 KD (see Figure 60 for the 20 kD conjugate) and that this is at least about 8 fold greater than the apparent size of the antibody fragment of 59 kD (see especially column 123 at lines 14-34). With respect to the unmutated Fab' fragment, the PEG is taught to be attached at the free Cys of the hinge region (see e.g., column 121 at lines 1-21).

Gonzalez et al. also teach that the PEG can be attached to a cysteine residue in the light or heavy chain of the antibody fragment that would ordinarily form the disulfide bridge linking the light and heavy chains, wherein the disulfide bridge is avoided by substituting another amino acid , such as serine, for the corresponding cysteine residue in the opposite chain (e.g., column 24 especially lines 46-58).

Gonzales et al. also teach that the Fab' can comprise a humanized anti-human IL-8 antigen binding site, including the complementarity determining regions of a light chain polypeptide amino acid sequence that is either 6G4V11N35A or 6G4V11N35E (e.g., columns 15 at lines 52-67, column 16 at lines 1-6, column 74 at lines 18-26, and claims).

Gonzales et al. also discloses conjugates further comprising avidin or biotin, i.e., nonproteinaceous label molecules (e.g., column 84 especially lines 9-19) or radiolabels (e.g., column 96 especially lines 20-31). Instant claims 33 and 34 are included in this rejection because Gonzalez et al. teach that, unless specifically indicated to the contrary, "conjugate" is defined as a heterogeneous molecule formed by the covalent attachment of one or more antibody fragment(s) to one or more polymer molecule(s) (especially column 12 at lines 56-60), i.e., it is an inherent property of the conjugate that its covalent structure is free of any matter other than the antibody fragment(s) and the polymer, i.e., PEG, molecule(s).

The reference teachings anticipate the claimed invention.

The rejection is maintained as applied to the amended claims.

12. Claims 1, 25-26, 28-29 and 31-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Gonzalez et a. (U.S. Patent No. 6,025,158, of record, see entire document).

Applicant does not directly argue the rejection of record in view of U.S. Patent No. 6,025,158, although it is noted that the section number of the previous Office Action was grouped with that of the preceding rejection. Thus at most Applicant argues that a Declarations under 37 CFR 1.132 by Leonard Presta and Steven Leong establishes that the "cited patent" is not "by another".

However, as noted supra, no Declarations under 37 CFR 1.132 were found attached to the instant Reply and no such Declarations are of record in the instant case.

As noted supra, it also is not clear from Applicant's comments if the Declarations were intended to be provided with respect to U.S. Patent No. 6,133,426, U.S. Patent No. 6,025,158, or both.

In the absence of the referenced Declarations, Applicant's argument that "the cited patent" is not "by another" is not found convincing.

The rejection of record is reiterated below as now applied to the amended claims:

Gonzales et al. teach a conjugate comprising an antibody Fab' (Fab'-SH) covalently attached to a single PEG molecule, wherein the PEG has an average molecular weight of at least about 20kD (see especially example T at columns 120-123) Gonzales et al. also teach that the conjugate of an antibody Fab' fragment and a single PEG is a conjugate that has an apparent size of at least about 500 KD (see Figure 60 for the 20 kD conjugate) and that this is at least about 8 fold greater than the apparent size of the antibody fragment of 59 kD (see especially column 122 at lines 31-54). With respect to the unmutated Fab' fragment, the PEG is taught to be attached at the free Cys of the hinge region (see e.g., column 120 at lines 15-37).

Gonzalez et al. also teach that the PEG can be attached to a cysteine residue in the light or heavy chain of the antibody fragment that would ordinarily form the disulfide bridge linking the light and heavy chains, wherein the disulfide bridge is avoided by substituting another amino acid , such as serine, for the corresponding cysteine residue in the opposite chain (e.g., column 25 especially lines 31-54).

Gonzales et al. also teach that the Fab' can comprise a humanized anti-human IL-8 antigen binding site, including the complementarity determining regions of a light chain polypeptide amino acid sequence that is either 6G4V11N35A or 6G4V11N35E (e.g., column 15 especially lines 42-65, columns 98-120, especially columns 113-120, and claims).

Gonzales et al. also discloses conjugates further comprising avidin or biotin, i.e., nonproteinaceous label molecules (e.g., column 83 at lines 48-58) or radiolabels (e.g., columns 95-96, especially column 95 at lines 55-67). Instant claims 33 and 34 are included in this rejection because Gonzalez et al. teach that, unless specifically indicated to the contrary, "conjugate" is defined as a heterogeneous molecule formed by the covalent attachment of one or more antibody fragment(s) to one or more polymer molecule(s) (especially column 12 at lines 53-65), i.e., it is an inherent property of the conjugate that its covalent structure is free of any matter other than the antibody fragment(s) and the polymer, i.e., PEG, molecule(s).

The reference teachings anticipate the claimed invention.

The rejection is maintained as applied to the amended claims.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1, 25, 31-33 and 36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata et al. (FASEB J. 1995, Abstract #1288, 9:A1479, IDS # 98) in view of Braxton (US Pat. No. 5,766,897, IDS #20).

Applicant's arguments, filed 12/30/02, have been fully considered but have not been found convincing, essentially for the reasons of record. Applicant's argument is addressed below in the context of the application of the rejection of record to the amended claims.

The claims are drawn to antibody Fab' fragments conjugated to single chain PEG of at least about 20 kD.

Zapata et al. teach a conjugate consisting essentially of a humanized anti-CD18 Fab' fragment covalently coupled via a sulfhydral group in the hinge region to a single chain PEG molecule (MePEG) that is either 5 kD or 10kD (see entire Abstract). Zapata et al. also teach that the Fab' fragment coupled to either size PEG did not interfere with the ability of the antibody to bind CD18, and reduced the clearance rate relative to the native Fab' molecule (Abstract middle). Zapata et al. note that the ability to extend the clearance rate of an antibody Fab' fragment without affecting antigen binding increased significantly the potential therapeutic value of the antibody (concluding remark).

Zapata et al. do not teach a conjugate in which the PEG is single chain molecule of at least about 20 kD.

However, Zapata et al. also note that although both the 5 kD and 10 kD forms of PEG reduced serum clearance, the 10 kD form of PEG was better than the 5 kD form (see last third of Abstract). Consequently, Zapata et al. clearly recognized that increasing the size of the PEG resulted in a further reduction the clearance rate. Thus the teaching of Zapata et al. establish that the size of the PEG molecule was a variable that affected the desirable property of reducing serum clearance rates, with a larger size producing a better effect.

Thus it would have been obvious to one of ordinary skill in the art to use higher molecular weight PEGs for covalent linkage to any Fab' antibody fragment for which one desired to reduce the serum clearance rate.

In addition, Braxton teach methods for the PEGylation of proteins by attaching a PEG molecule via the thiol group on a free cysteine (see entire document, e.g., column 12 especially lines 48-50). Braxton teach that the molecular weight of the attached PEG may be from 200 to 20,000 MW (i.e., from about 0.2 to 20 kD) and that particularly for relatively small proteins that generally have short half lives and because of their small size have fewer PEG sites available, the PEG moiety used should be of a higher molecular weight (see especially lines 48-65). Since Braxton does not stipulate that the PEG is a branched chain polymer, the PEG taught by Braxton is also a single chain molecule. Braxton also teaches formulation of the PEGylated proteins in a pharmaceutical composition comprising a carrier (e.g., columns 24-28). Although it is not explicitly stated that the pharmaceutical composition was sterile, sterility is requisite for therapeutics and so would have been obvious to one of ordinary skill in the art at the time the invention was made.

Applicant acknowledges that Zapata et al. teach that nonspecific clearance of an antibody Fab' fragment can be decreased by site-directed addition of a PEG moiety. However, Applicant argues in view of the full poster presentation associated with the cited Zapata et al. Abstract (current IDS # 97) and in view of Knauf (J. Biol. Chem. 1988; 263:15064-15070, IDS#70) that the decreased clearance observed as the effective molecular weight increased towards 70kD was due to the fact that the glomerular filtration cutoff size is approximately 70kD. Applicant concludes that the ordinary artisan at the time the invention was made would therefore NOT have been motivated to make and use antibody-PEG conjugates with apparent molecular weights of at least about 500kD.

However, the Examiner notes that both Zapata et al. (e.g., point 8 of the Poster Discussion) and Knauf et al. (e.g., page 15069, 1st partial paragraph) acknowledge that glomerular filtration is not the only mechanism of clearance which can be reduced by PEGylation of proteins.

Thus the Examiner maintains that given the guidance provided by Braxton that higher molecular weight PEGs should be used when only a few coupling sites are available on relatively small proteins, such as the Fab' antibody fragments taught by Zapata et al.; and the identification by Braxton of 20 kD as being the upper end of the molecular weight range of PEGs taught; it would have been obvious to the ordinary artisan at the time the invention was made to select a 20 kD PEG for use in coupling to relatively small proteins, including the Fab' antibody fragments as taught by Zapata et al. Given the simple substitution of a higher molecular weight PEG, the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing a humanized anti-CD18 Fab' fragment covalently coupled to a single 20 kD single chain PEG.

Given the teachings of Zapata et al., particular in view of the teachings of Braxton, the ordinary artisan would have been motivated to formulate such a conjugate in order to further reduce the serum clearance of a therapeutic antibody. Although the references are silent with respect to the apparent size of the conjugate and the relationship of the apparent size of the conjugate to that of the unconjugated Fab' fragment; given that the same product is produced (an Fab' fragment coupled to a 20 kD single chain PEG), that product would necessarily have an apparent size of at least about 500 kD and that would be at least about 8 fold greater than the apparent size of at least one antibody fragment. It is noted that motivation existed for substituting the 20kD PEG into the Fab'-PEG conjugate taught by Zapata et al.; thus no motivation is required for the ordinary artisan to select based upon an apparent size of at least about 500 kD and at least about 8 fold greater apparent size; motivation to select a 20kD PEG would necessarily result in these properties without any appreciation of them by the ordinary artisan.

Finally, one of ordinary skill in the art at the time the invention was made would have been motivated to produce a conjugate, wherein the covalent structure of said conjugate was free of any matter other than the antibody fragment and the nonproteinaceous polymer to insure purity, potency and sterility of the conjugate for therapeutic use. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is maintained as applied to the amended and newly added claims.

15. Claims 26 and 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata et al. (FASEB J. 1995, Abstract #1288, 9:A1479, IDS # 98) in view of Braxton (US Pat. No. 5,766,897, IDS #20) as applied to claims 1, 25, 31-33 and 36 above, and further in view of Doerschuk et al (U.S. Patent No. 5,702,946, IDS #18).

Applicant's arguments with respect to the instant rejection are that Doerschuk et al. does not correct the deficiencies of Zapata et al. in view of Braxton et al.

Applicant's arguments regarding Zapata et al. in view of Braxton et al. have not been found convincing for the reasons set forth supra.

The claims are still drawn to anti-IL-8 and humanized anti-IL-8 Fab' fragments conjugated to single chain PEG of at least about 20 kD.

Zapata et al. in view of Braxton have been discussed supra.

Zapata et al. in view of Braxton do not teach that an antibody Fab' fragment that binds to human IL-8.

Doerschuk et al. teach anti-IL-8 monoclonal antibodies and Fab' fragments of these antibodies, as well as humanized anti-IL-8 antibodies and humanized anti-IL-8 Fab' fragments (see entire document, e.g. columns 1-2 and claims). Doerschuk et al. also teach the use of the anti-IL-8 antibody and humanized antibody fragments for treatment and diagnosis of inflammatory disorders (e.g., columns 13-14). Thus Doerschuk et al. establish that anti-IL-8 antibodies, including humanized anti-IL-8 antibodies are therapeutically and diagnostically valuable.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention by substituting the anti-IL-8 Fab' fragments of Doerschuk et al. for the anti-CD18 Fab' conjugate taught by Zapata et al. in view of Braxton. One of ordinary skill in the art would have been motivated to add PEG to an anti-IL-8 Fab' fragment using the method of Zapata et al. and Braxton because Doerschuk et al. teach the usefulness of anti-IL-8 monoclonal antibody Fab' fragments in treatment and diagnosis of inflammatory disorders and because both Zapata et al. and Braxton teach that addition of PEG reduces serum clearance of therapeutics and reduces immunogenicity. Given the availability of the anti-IL-8 Fab' fragment and the methods of adding PEG, including a 20kD single chain PEG to an antibody Fab' fragment, the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing the instant invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is therefore maintained as applied to the amended claims.

16. Claims 34 and 35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata et al. (FASEB J. 1995, Abstract #1288, 9:A1479, IDS # 98) in view of Braxton (US Pat. No. 5,766,897, IDS #20) as applied to claims 1, 25, 31-33 and 36 above, and further in view of Griffiths et al (U.S. Patent No. 5,670,132, IDS #13).

Applicant's arguments with respect to the instant rejection are that Doerschuk et al. does not correct the deficiencies of Zapata et al. in view of Braxton et al.

Applicant's arguments regarding Zapata et al. in view of Braxton et al. have not been found convincing for the reasons set forth supra.

The claims are still drawn to Fab' fragments conjugated to single chain PEG of at least about 20 kD and incorporating into the covalent structure of the conjugate one or more radiolabels.

Zapata et al. in view of Braxton have been discussed supra.

Zapata et al. in view of Braxton do not teach antibody fragment-PEG conjugates that are radiolabeled.

Griffiths et al. teach a radiolabeled Fab'-PEG conjugate which includes in the covalent structure of the conjugate a radiolabel (see entire document, e.g., Abstract). Griffiths et al. also teach the use of the radiolabeled conjugate in in vivo diagnostics (see column 1, last paragraph and column 2, last paragraph and continuing onto column 3). Griffiths et al. teach that coupling of PEG to Fab' fragments is desirable because addition of PEG to an Fab' avoids the accumulation of Fab' fragments in the kidney and thereby improves the use of Fab' fragments in in vivo diagnostics (e.g., column 1, especially lines 46-60), in addition to an art recognized benefit of reducing the rate of serum clearance (e.g., column 1 especially lines 52-54),. Griffiths et al. also teach conjugates that are to be administered internally to a patient (other than oral administration) are stored under sterile conditions and administered in sterile pharmaceutically acceptable carriers (especially column 5, lines 45-61).

It would therefore have been obvious to one of ordinary skill in the art at the time the invention was made to label the Fab'-PEG 20 kD conjugate as taught by Zapata et al. and Braxton, with a radiolabel as taught by Griffiths et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in light of Griffiths teaching that the addition of a radiolabel permits in vivo diagnostic use of antibody Fab' fragments; and in view of the teachings of Zapata et al. and Braxton with respect to the reduced serum clearance of 20kD PEG compared to the smaller 5 kD PEG exemplified by Griffiths et al. One of ordinary skill in the art at the time the invention was made would have been motivated to produce a conjugate, wherein the covalent structure of said conjugate was free of any matter other than the antibody fragment, the nonproteinaceous polymer and the label molecule to insure purity and potency of the conjugate for in vivo diagnostic use. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1, 25-26, 28-29 and 31-36 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 10-13, 15-19, 21, 24-26 and 28-34 of copending Application No. USSN 09/355,014. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '014 application recite all the limitations recited in the instant claims, indicating that the limitations set forth in the instant claims were obvious embodiments of the invention claimed in USSN 09/355,014.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's comments regarding their readiness to file a Terminal Disclaimer as appropriate once allowable subject matter is identified are acknowledged.

The rejection is however maintained until such time as the Terminal Disclaimer is filed or the rejection is obviated.

19. Applicant's provision of evidence that USSN 09/355,014 and present application USSN 09/726258 were subject to assignment to the same entity, Genentech, Inc., at the time the present invention was made is acknowledge.

Conclusion

20. No claim is allowed.

21. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
March 19, 2003

Phillip Gambel
PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
3/22/03